

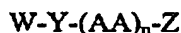
Application No. 09/937,150

Reply to Office Action

*AMENDMENTS TO THE CLAIMS*RECEIVED
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1-38. (Canceled)

39. (Currently Amended) A compound of the formula:



wherein n is 1 to 15;

Y is a phenylalanyl radical having a phenyl ring, an amine end, a carboxyl end, and a $-CH_2CH<$ group attached to the phenyl ring at the $-CH_2$ and the amine end and the carboxyl end attached to the CH<, the phenyl ring having one or more substituents selected from the group consisting of hydroxyl, carboxyl, formyl, carboxyalkyl, carboxyalkyloxy, dicarboxyalkyl, dicarboxyalkyloxy, dicarboxyhaloalkyl, dicarboxyhaloalkyloxy, and phosphonoalkyl, phosphonohaloalkyl, wherein the alkyl portion of the substituents of the phenyl ring may be unsubstituted or substituted with a substituent selected from the group consisting of halo, hydroxy, carboxyl, amino, aminoalkyl, alkyl, and alkoxy;

W is a moiety attached to the nitrogen of Y and is selected from the group consisting of alkylcarbonyl, oxalyl, alkylaminooxalyl, arylaminooxalyl, arylalkylaminooxalyl, alkoxyoxalyl, carboxyalkyl carbonyl, heterocyclyl carbonyl, heterocyclylalkyl carbonyl, arylalkyl heterocyclylalkyl carbonyl, aryloxy carbonyl, and arylalkoxy carbonyl, wherein the aryl and alkyl portions of W may be unsubstituted or substituted with a substituent selected from the group consisting of halo, hydroxy, aminoalkyl, alkyl, and alkoxy; and the heterocyclyl portion of W contains at least 4 hetero atoms selected from the group consisting of O, N, and S;

AA is an amino acid, the amine end of which is attached to the carboxyl end of Y; and

Z is arylalkylamino or aryl heterocyclyl C_1-C_6 alkylamino wherein an aryl group, which may be substituted or unsubstituted, is linked to a heterocyclyl group; wherein aryl is a carbocyclic aryl;

or a salt thereof;

with the proviso that Z is not arylalkylamino when W is oxalyl or acetyl and the phenyl ring of phenylalanyl contains a hydroxyl, malonyl difluoromethyl, malonyloxy, carboxyalkyloxy, phosphonodifluoromethyl, or phosphonomethyl substituent on the phenyl ring at a position para to the $-CH_2CH<$ group and the ortho and meta positions are unsubstituted and the proviso that Z is not arylalkylamino when W is arylalkoxy carbonyl and the ~~substituent~~ substituent on the phenyl ring of Y is phosphonomethyl.

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40. (Currently Amended) A compound of the formula: $W-Y-(AA)_n-Z$ wherein n is 1 to 15;

Y is a phenylalanyl radical having a phenyl ring, an amine end, a carboxyl end, and a $-CH_2CH<$ group attached to the phenyl ring at the $-CH_2$ and the amine end and the carboxyl end attached to the $CH<$, the phenyl ring having one or more substituents selected from the group consisting of hydroxyl, carboxyl, formyl, carboxy C_1-C_6 alkyl, carboxy C_1-C_6 alkyloxy, dicarboxy C_1-C_6 alkyl, dicarboxy C_1-C_6 alkyloxy, dicarboxyhalo C_1-C_6 alkyl, dicarboxyhalo C_1-C_6 alkyloxy, and phosphono C_1-C_6 alkyl, phosphonohalo C_1-C_6 alkyl, wherein the alkyl portion of the substituents of the phenyl ring may be unsubstituted or substituted with a substituent selected from the group consisting of halo, hydroxy, carboxyl, amino, aminoalkyl, C_1-C_6 alkyl, and C_1-C_6 alkoxy;

W is a moiety attached to the nitrogen of Y and is selected from the group consisting of C_1-C_6 alkylcarbonyl, oxalyl, C_1-C_6 alkylaminooxalyl, arylaminooxalyl, aryl C_1-C_6 alkylaminooxalyl, C_1-C_6 alkoxyoxalyl, carboxy C_1-C_6 alkyl carbonyl, heterocyclyl carbonyl, heterocyclyl C_1-C_6 alkyl carbonyl, aryl C_1-C_6 alkyl heterocyclyl C_1-C_6 alkyl carbonyl, aryloxy carbonyl, and aryl C_1-C_6 alkoxy carbonyl, wherein the aryl and alkyl portions of W may be unsubstituted or substituted with a substituent selected from the group consisting of halo, hydroxy, amino C_1-C_6 alkyl, C_1-C_6 alkyl, and C_1-C_6 alkoxy; and the heterocyclyl portion of W contains at least 4 hetero atoms selected from the group consisting of O, N, and S;

AA is an amino acid, the amine end of which is attached to the carboxyl end of Y ; and

Z is aryl C_1-C_6 alkylamino or arylheterocyclyl C_1-C_6 alkylamino wherein an aryl group is linked to a heterocyclyl group; wherein aryl is a carbocyclic aryl group; or a salt thereof;

with the proviso that Z is not aryl C_1-C_6 alkylamino when W is oxalyl or acetyl and the phenyl ring of phenylalanyl contains a hydroxyl, dicarboxyhaloalkyl, dicarboxyalkoxy, carboxyalkyloxy, phosphonoalkyl, or phosphonohaloalkyl substituent of the phenyl ring at a position para to the $-CH_2CH<$ group and the ortho and meta positions are unsubstituted and the proviso that Z is not arylalkylamino when W is aryl methoxycarbonyl when the ~~substituent~~ substituent on the phenyl ring of Y is phosphonomethyl.

41. (Previously Presented) A compound of the formula:

$W-Y-(AA)_n-Z$ wherein n is 1 to 15;

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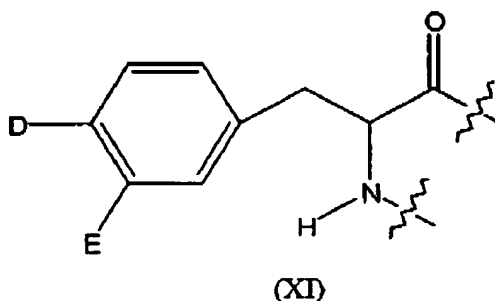
W is a moiety attached to the nitrogen of Y and is selected from the group consisting of C₁-C₆ alkylcarbonyl, oxalyl, C₁-C₆ alkylaminooxalyl, arylaminooxalyl, aryl C₁-C₆ alkylaminooxalyl, C₁-C₆ alkoxyoxalyl, carboxy C₁-C₆ alkyl carbonyl, heterocyclyl carbonyl, heterocyclyl C₁-C₆ alkyl carbonyl, aryl C₁-C₆ alkyl heterocyclyl C₁-C₆ alkyl carbonyl, aryloxy carbonyl, and aryl C₁-C₆ alkoxy carbonyl, wherein the aryl and alkyl portions of W may be unsubstituted or substituted with a substituent selected from the group consisting of halo, hydroxy, carboxyl, amino, amino C₁-C₆ alkyl, C₁-C₆ alkyl, and C₁-C₆ alkoxy; and the heterocyclyl portion of W contains at least 4 hetero atoms selected from the group consisting of O, N, and S;

AA is an amino acid, the amine end of which is attached to the carboxyl end of Y; and

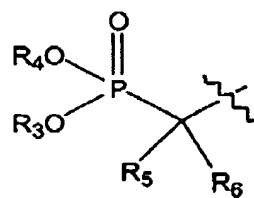
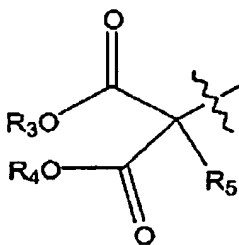
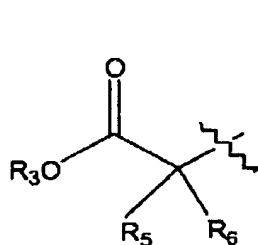
Z is aryl C₁-C₆ alkylamino or arylheterocyclyl C₁-C₆ alkylamino wherein an aryl group is linked to a heterocyclyl group; wherein aryl is a carbocyclic aryl group;

or a salt thereof;

wherein Y is of the formula XI:



wherein D has the formula XII, XIII, or XIV:



wherein R₃ and R₄ may be the same or different and are selected from the group consisting of hydrogen, C₁-C₆ alkyl, aryl, aryl C₁-C₆ alkyl, C₁-C₆ alkaryl, and heteroaryl; and R₅ and R₆

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may be the same or different and are selected from the group consisting of hydrogen, halo, hydroxy, amino, and C₁-C₆ alkoxy; and

E is selected from the group consisting of hydrogen, C₁-C₆ alkyl, C₁-C₆ alkylcarbonyl, carboxyl, and C₁-C₆ alkylcarbonyl C₁-C₆ alkyl;

with the proviso that Z is not aryl C₁-C₆ alkylamino when W is oxalyl or acetyl and D is hydroxyl, dicarboxyhaloalkyl, dicarboxyalkoxy, carboxyalkyloxy, alkoxycarbonylalkyl, phosphonoalkyl, or phosphonohaloalkyl and E is hydrogen.

42. (Previously Presented) The compound of claim 41, wherein D is of formula XII.

43. (Previously Presented) The compound of claim 41, wherein D is of formula XIII.

44. (Previously Presented) The compound of claim 41, wherein D is of formula XIV.

45. (Previously Presented) The compound of claim 42, wherein E is hydrogen.

46. (Previously Presented) The compound of claim 42, wherein E is carboxyl.

47. (Previously Presented) The compound of claim 42, wherein R₃, R₅, and R₆ are hydrogen.

48. (Previously Presented) The compound of claim 44, wherein R₃ and R₄ are hydrogen.

49. (Previously Presented) The compound of claim 39, wherein W is selected from the group consisting of C₁-C₆ alkylcarbonyl, oxalyl, C₁-C₆ alkylaminooxalyl, arylaminooxalyl, aryl C₁-C₆ alkylaminooxalyl, C₁-C₆ alkoxyoxalyl, carboxy C₁-C₆ alkyl carbonyl, heterocyclyl carbonyl, heterocyclyl C₁-C₆ alkyl carbonyl, aryl C₁-C₆ alkyl heterocyclyl C₁-C₆ alkyl carbonyl, aryloxycarbonyl, and aryl C₁-C₆ alkoxycarbonyl, wherein the aryl and alkyl portions of W may be unsubstituted or substituted with a substituent selected from the group consisting of halo, hydroxy, carboxyl, amino, amino C₁-C₆ alkyl, C₁-C₆ alkyl, and C₁-C₆ alkoxy; and the heterocyclyl portion of W contains at least 4 hetero atoms selected from the group consisting of O, N, and S.

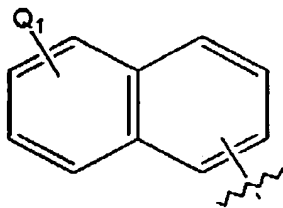
50-66. (Canceled)

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67. (Previously Presented) The compound of claim 40, wherein Z is aryl C₁-C₆ alkylamino.

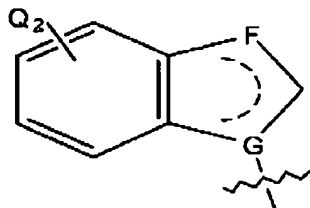
68. (Previously Presented) The compound of claim 67, wherein the aryl portion of Z has the formula:



wherein Q₁ is hydrogen or a substituent selected from the group consisting of hydroxyl, halo, C₁-C₆ alkyl, C₁-C₆ alkoxy, amino, and C₁-C₆ acylamino.

69-72. (Canceled)

73. (Previously Presented) The compound of claim 39, wherein the aryl heterocyclyl portion of Z has the formula:



wherein Q₂ is hydrogen or a substituent selected from the group consisting of hydroxyl, halo, C₁-C₆ alkyl, C₁-C₆ alkoxy, amino, and C₁-C₆ acylamino, and F and G are independently selected from the group consisting of C, N, O, and S; with the proviso that F and G are not simultaneously C.

74-77. (Canceled)

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78. (Previously Presented) The compound of claim 39, wherein said amino acid is selected from the group consisting of glycine, alanine, valine, norvaline, leucine, iso-leucine, norleucine, α -amino n-decanoic acid, serine, homoserine, threonine, methionine, cysteine, S-acetylaminoethyl-cysteine, proline, trans-3- and trans-4-hydroxyproline, phenylalanine, tyrosine, 4-aminophenylalanine, 4-nitrophenylalanine, 4-chlorophenylalanine, 4-carboxyphenylalanine, β -phenylserine β -hydroxyphenylalanine, phenylglycine, α -naphthylalanine, cyclohexylalanine, cyclohexylglycine, tryptophan, indoline-2-carboxylic acid, 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, aspartic acid, asparagine, aminomalonic acid, aminomalonic acid monoamide, glutamic acid, glutamine, histidine, arginine, lysine, N'-benzyl-N'-methyl-lysine, N',N'-dibenzyl-lysine, 6-hydroxylysine, ornithine, α -aminocyclopentane carboxylic acid, α -aminocyclohexane carboxylic acid, α -aminocycloheptane carboxylic acid, α -(2-amino-2-norbornane)-carboxylic acid, α,γ -diaminobutyric acid, α,β -diaminopropionic acid, homophenylalanine, and α -tert-butylglycine.

79-84. (Canceled)

85. (Previously Presented) A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of claim 39.

86-115. (Canceled)

116. (Previously Presented) A compound of the formula:



wherein n is 0 to 15;

Y is a phenylalanyl radical having a phenyl ring, an amine end, and a carboxyl end, a $-\text{CH}_2\text{CH}<$ group attached to the phenyl ring at the CH_2 and the amine end and the carboxyl end are attached to the $\text{CH}<$, the phenyl ring having the following substituent or a combination of substituents: (i) dicarboxy C_1 - C_6 alkyl, (ii) hydroxyl and carboxy C_1 - C_6 alkyl, (iii) carboxyl and carboxy C_1 - C_6 alkyl, or (iv) dicarboxyhalo C_1 - C_6 alkyloxy; or an ester of (i), (ii), (iii), or (iv); wherein the alkyl portion of the substituents of the phenyl ring may be unsubstituted or substituted with a substituent selected from the group consisting of hydroxy, carboxyl, amino, aminoalkyl, C_1 - C_6 alkyl, and C_1 - C_6 alkoxy;

W is a moiety attached to the nitrogen of Y and is selected from the group consisting of C_1 - C_6 alkylcarbonyl, oxalyl, C_1 - C_6 alkylaminooxalyl, arylaminooxalyl, aryl C_1 - C_6 alkylaminooxalyl, C_1 - C_6 alkoxyoxalyl, carboxy C_1 - C_6 alkyl carbonyl, heterocyclyl carbonyl,

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heterocyclyl C₁-C₆ alkyl carbonyl, aryl C₁-C₆ alkyl heterocyclyl C₁-C₆ alkyl carbonyl, aryloxy carbonyl, and aryl C₁-C₆ alkoxy carbonyl, wherein the aryl and alkyl portions of W may be unsubstituted or substituted with a substituent selected from the group consisting of halo, hydroxy, carboxyl, amino, amino C₁-C₆ alkyl, C₁-C₆ alkyl, and C₁-C₆ alkoxy; and the heterocyclyl portion of W contains at least 4 hetero atoms selected from the group consisting of O, N, and S;

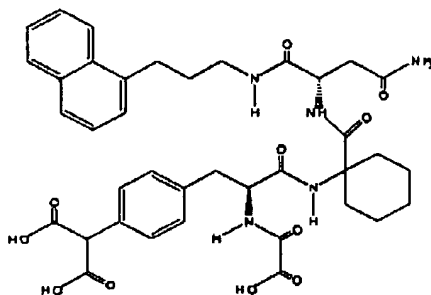
AA is an amino acid, the amine end of which is attached to the carboxyl end of Y; and

Z is aryl C₁-C₆ alkylamino or arylheterocyclyl C₁-C₆ alkylamino wherein an aryl group is linked to a heterocyclyl group; wherein aryl is a carbocyclic aryl; or a salt thereof.

117. (Previously Presented) A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of claim 116.

118-119. (Canceled)

120. (Previously Presented) The compound of claim 39, which is of the formula:



121. (Previously Presented) A pharmaceutical composition comprising a pharmaceutically acceptable carrier and the compound of claim 120.

122. (Previously Presented) A method for inhibiting an SH2 domain of a protein from binding with a phosphoprotein comprising contacting the SH2 domain with the compound of claim 120.

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123. (Previously Presented) A method of inhibiting Grb2 signaling in a cancer cell in a patient comprising contacting the cell with the compound of claim 120.
124. (Previously Presented) A method of inhibiting MAP kinase activity in a mammal comprising administering to the mammal in need thereof the compound of claim 120.
125. (Canceled)
126. (Previously Presented) The compound of claim 116, wherein n is 1-3.
127. (Previously Presented) The compound of claim 116, wherein Z is naphthylpropylamino.
128. (Previously Presented) The compound of claim 116, wherein the phenyl ring of Y includes a malonyl group.
129. (Previously Presented) The compound of claim 116, wherein the phenyl ring of Y includes a carboxymethyl group and a hydroxyl group.
130. (Previously Presented) The compound of claim 116, wherein said amino acid is selected from the group consisting of glycine, alanine, leucine, isoleucine, norleucine, cyclohexylalanine, 4-aminocyclohexylglycine, 4-acetylaminocyclohexylglycine, aspartic acid, asparagine, glutamic acid, and glutamine.
- 131-132. (Canceled)
133. (Previously Presented) A method for treating breast cancer in a patient comprising administering to the patient an effective amount of the compound of claim 120.
- 134-135. (Canceled)
136. (Previously Presented) A method of enhancing the therapeutic effect of a breast cancer treatment rendered to a mammal that has been afflicted with breast cancer, comprising

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administering to the mammal the compound of claim 120 in conjunction with the treatment, wherein the treatment comprises chemotherapy, radiation therapy, or biological therapy.

137-139. (Canceled)

140. (Previously Presented) A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of claim 40.

141. (Previously Presented) A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of claim 41.

142. (Previously Presented) A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of claim 42.

143. (Previously Presented) A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of claim 43.

144. (Previously Presented) A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of claim 44.

145. (Previously Presented) A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of claim 49.

146. (Previously Presented) A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of claim 68.

147. (Previously Presented) A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of claim 73.

148. (Previously Presented) A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of claim 78.

149. (Previously Presented) A method for inhibiting an SH2 domain of a protein from binding with a phosphoprotein comprising contacting the SH2 domain with the compound of claim 39.

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150. (Previously Presented) A method for inhibiting an SH2 domain of a protein from binding with a phosphoprotein comprising contacting the SH2 domain with the compound of claim 40.

151. (Previously Presented) A method for inhibiting an SH2 domain of a protein from binding with a phosphoprotein comprising contacting the SH2 domain with the compound of claim 41.

152. (Previously Presented) A method of inhibiting Grb2 signaling in a cancer cell in a patient comprising contacting the cell with a compound of claim 39.

153. (Previously Presented) A method of inhibiting Grb2 signaling in a cancer cell in a patient comprising contacting the cell with a compound of claim 40.

154. (Previously Presented) A method of inhibiting Grb2 signaling in a cancer cell in a patient comprising contacting the cell with a compound of claim 41.

155. (Previously Presented) A method for inhibiting the growth of human breast cancer cells comprising contacting the cells with a compound of claim 39.

156. (Previously Presented) A method for inhibiting the growth of human breast cancer cells comprising contacting the cells with a compound of claim 40.

157. (Previously Presented) A method for inhibiting the growth of human breast cancer cells comprising contacting the cells with a compound of claim 41.

158. (Previously Presented) A method for inhibiting the growth of human breast cancer cells comprising contacting the cells with a compound of claim 116.